Evidence for a subcortical origin of mirror movements after stroke: a longitudinal study

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Abstract: Following a stroke, mirror movements are unintended movements that appear in the non-paretic hand when the paretic hand voluntarily moves. Mirror movements have previously been linked to overactivation of sensorimotor areas in the non-lesioned hemisphere. In this study, we hypothesized that mirror movements might instead have a subcortical origin, and are the by-product of subcortical motor pathways upregulating their contributions to the paretic hand. To test this idea, we first characterized the time course of mirroring in 53 first-time stroke patients, and compared it to the time course of activities in sensorimotor areas of the lesioned and non-lesioned hemispheres (measured using functional MRI). Mirroring in the non-paretic hand was exaggerated early after stroke (Week 2), but progressively diminished over the year with a time course that parallelled individuation deficits in the paretic hand. We found no evidence of cortical overactivation that could explain the time course changes in behaviour, contrary to the cortical model of mirroring. Consistent with a subcortical origin of mirroring, we predicted that subcortical contributions should broadly recruit fingers in the non-paretic hand, reflecting the limited capacity of subcortical pathways in providing individuated finger control. We therefore characterized finger recruitment patterns in the non-paretic hand during mirroring. During mirroring, non-paretic fingers were broadly recruited, with mirrored forces in homologous fingers being only slightly larger (1.76 times) than those in non-homologous fingers. Throughout recovery, the pattern of finger recruitment during mirroring for patients looked like a scaled version of the corresponding control mirroring pattern, suggesting that the system that is responsible for mirroring in controls is upregulated after stroke. Together, our results suggest that post-stroke mirror movements in the non-paretic hand, like enslaved movements in the paretic hand, are caused by the upregulation of a bilaterally organized subcortical system.

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Evolution of mirror movements after stroke reveals interactions between descending motor pathways involved in hand function

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Behavioural dataset available at:

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Abstract

In primates, an interaction between cortical and subcortical pathways is responsible for the control and recovery of hand function after a stroke. Motor circuits associated with these pathways provide a certain degree of functional specialization, with subcortical circuits providing gross, synergistic recruitment of muscles while cortical circuits provide the ability to selectively control a few muscles to produce highly fractionated finger movements. To what extent is hand function (and functional recovery after stroke) mediated by similar interactions between cortical and subcortical pathways in humans? Here, we demonstrate that mirror movements that appear after stroke offer a window through which these interactions can potentially be assessed. Mirror movements are the involuntary movements on the non-paretic hand when the paretic hand is actively moved. Using a sensitive behavioural assay, we quantified changes in mirroring and paretic hand function in 53 first-time patients in the year following unilateral stroke. Mirror movements appeared early after stroke (week 2), and progressively normalized over the year with a time-course that mimicked that for the deficits in fine-finger control in the paretic hand. Individuated finger presses with the paretic hand, resulted in a broad recruitment of fingers on the non-paretic hand, with mirroring observed in both the mirror-symmetric (homologous) and heterologous finger pairs. Despite this broad recruitment of fingers during mirroring, the associated effects in homologous fingers were (on average) larger than heterologous pairs. We propose that this pattern of recruitment of fingers during mirroring is best explained by summed contributions from motor circuits in cortical and subcortical areas. A closer examination of mirroring in the paretic hand provided further evidence of this view. Together, our results suggest that hand function in humans – like in primates – is controlled by the interaction between cortical and subcortical motor pathways.

Key words: mirror movements, finger movements, post-stroke recovery

Introduction

The neural reorganization processes that occur after stroke and promote the recovery of hand function remain a mystery. Insights can be derived from primate work, which suggest that a substantial part of reorganization involves changes in the relative contributions of the different motor pathways towards hand control (Baker, 2011b; Lawrence and Kuypers, 1968a; 1968b; Lemon, 2008; Tower, 1940; Zaaimi *et al.*, 2012). In primates, motoneurons and spinal interneurons that innervate distal hand muscles receive input from multiple descending motor pathways. Of these, primary input comes from the motor circuits in the contralateral hemisphere via the crossed corticospinal tract (Porter and Lemon, 1993; Soteropoulos *et al.*, 2011), with the pathway considered critical for generating fine-finger movements (Lawrence and Kuypers, 1968a; e.g. pincer grasp; Tower, 1940). Additional input comes from phylogenetically-older motor circuits in the brainstem (Riddle *et al.*, 2009). Partly under cortical control (Fisher *et al.*, 2012), these motor pathways are mainly responsible for controlling gross movements (e.g. whole-hand grasping), and offer only a limited ability for selective, fractionated finger control (Lawrence and Kuypers, 1968b; Soteropoulos *et al.*, 2012). Together these different pathways appear to offer a certain degree of control redundancy, with reorganization and strengthening of subcortical-spinal connections being able to (partly) counterbalance the effects of cortical damage (Lawrence and Kuypers, 1968b; Zaaimi *et al.*, 2012). In man, the extent to which (if at all) hand function and recovery after stroke is mediated by similar interactions between cortical and subcortical pathways is unknown (but see, Xu *et al.*, 2016).

Here, we demonstrate that characterizing mirror movements that appear after stroke, offers insights into the relative contributions of different pathways towards hand control and recovery that cannot be obtained by studying deficits on the paretic hand alone. In the context of hand function after stroke, mirror movements are the involuntary movements that appear on the fingers of the non-paretic hand when the paretic hand is actively moved (Cernacek, 1961; Y. Kim *et al.*, 2015; Nelles *et al.*, 1998; Sehm *et al.*, 2009). Since mirror movements have exclusively been studied in patients with chronic stroke, it remains to be determined whether they first appear in the early or late stages of recovery. An early appearance could be caused by stroke-related damage to the different motor pathways,

resulting in abnormal input to motoneurons/spinal interneurons that control the non-paretic hand. Alternatively, mirroring might be a compensatory effect: a by-product of increased reliance on alternative motor circuits (e.g. brainstem/non-lesioned hemisphere) for the recovery of paretic hand function. These two possibilities would predict very different time-courses for the emergence of mirroring, with the first predicting their presence early after insult, while the later suggesting a more progressive appearance during recovery. Therefore, our first aim was to carefully characterize the time course of mirror movements on the non-paretic hand after stroke.

A closer examination of the nature of mirroring across the fingers of the non-paretic hand may provide additional insights into cortical and subcortical contributions to hand function during recovery. Mirror movements can potentially occur in one of two forms, strong or weak. In its stronger form, mirroring effects during individuated finger movements should largely be restricted to the finger homologous to the instructed finger, with minimal effects on heterologous finger pairs. In contrast, the weaker form would be characterized by a diffuse recruitment of multiple fingers, with mirroring effects approximately balanced across homologous and heterologous finger pairs. The presence of stronger and weaker forms of mirroring can serve as strong identifiers of the motor circuits and pathways that caused them. As fine-finger movements are considered to be (almost) exclusively controlled by cortical circuits (Brinkman and Kuypers, 1973; Soteropoulos *et al.*, 2011), purely homologous mirroring on the non-paretic hand would largely rule out a subcortical locus for the effect. If, however, mirroring effects on the non-paretic hand were nearly equal for homologous and heterologous finger pairs, a role for subcortical pathways in the generation of mirror movements must be considered. Our second aim, therefore, was to quantify mirror movements separately for homologous and heterologous finger pairs on the non-paretic hand.

To fulfill the two aims of our study, we used a sensitive behavioural assay to characterize mirror movements in a large cohort of stroke patients for a year after stroke. Overall, our results suggest that mirror movements – and by association hand function - are controlled by interactions between cortical and subcortical motor pathways. Finally, we using fMRI, we demonstrate that over-activation of cortical motor areas is not the mechanism by which mirror movements are exaggerated after stroke.

Materials and Methods

Participants

A large cohort of 53 patients with hemiparesis (20 female; age=57.4, SD=14.9 years) was recruited within the first week after stroke. The recovery of strength and individuation of the paretic hand is reported in a separate paper (Xu *et al.*, 2016), but clinical measures of hand function are summarized in Supplementary Figure 1 and show that patients had a broad distribution of hand impairments at the time of recruitment. Patients were only included if they had a first ever unilateral ischemic stroke within the previous 2 weeks and reported unilateral weakness of the upper extremity (Medical Research Council muscle weakness scale<5). They were excluded if they were less than 21 years of age, their initial upper-limb impairment was too mild (Fugl-Meyer>63/66), or if they had cognitive deficits that could impair their comprehension and performance in the task. The exclusion of aphasic patients led to a bias of right-hemispheric infarcts in the patient cohort (36 right, 17 left). The lesions affected either the cortical grey matter in the region of the central sulcus (N=27), or the cortical-fugal white matter tracks in the corona radiata or internal capsule (N=43). None of the patients had lesions in the brainstem.

A total of 14 neurologically-healthy participants were also recruited as part of the study and served as controls (4 female; age=64.0, SD=8.2 years). Controls and patients were matched for age (t_{65}=1.60, p=0.11). According to the Edinburgh questionnaire (Oldfield, 1971), all 14 controls were right handed, while 42 patients were right- and 11 were left-handed.

Data for the study was collected across three centres: Johns Hopkins University, University of Zurich, and Columbia University. All experimental procedures were approved by the respective local ethics committee, and written consent was obtained from both patients and controls.

Apparatus to measure finger forces

We used a custom-built fMRI compatible keyboard (Fig. 1A) to continuously measure isometric finger forces generated during the behavioural and fMRI tasks. During either experiment, participants were seated comfortably and were instructed to keep both their hands on the 10 piano-like keys of the device at all times, each of which was

equipment with a force transducer (Honeywell FS Series, dynamic range 0-25 N). This apparatus allowed for the sensitive measurement of the forces generated on the instructed hand during finger presses (Fig. 1B), as well as the resulting mirrored forces on the fingers of the passive hand (Diedrichsen *et al.*, 2013; Ejaz *et al.*, 2015).

Assessment of mirror movements during the behavioural task

The degree of mirroring exhibited by each participant (patients and controls) was assessed over five longitudinal measurement sessions following recruitment (Table 1); within the first 2 weeks (week 2), at 4-6 weeks (week 4), 12-14 weeks (week 12), 24-26 weeks (week 24) and 52-54 weeks (week 52).

During each measurement session, participants performed individuated isometric force presses with the instructed finger on the active hand, while mirrored forces on the fingers of the passive hand were recorded. A visual representation of all ten fingers was presented on a computer screen (Fig. 1A). The experiment began by estimating the strength of each finger, by measuring 2 repetitions of the maximum voluntary force of each digit on either hand. All subsequent trials required the production of isometric fingertip forces at a fraction of the maximal force for the instructed digit (at 20%, 40%, 60% and 80%).

At the start of every trial, a force target-zone on a single finger was highlighted in green. This was the cue for participants to make a short isometric force press with the instructed finger to match and maintain the target-zone force (target force±25%) for 0.5s. The trial was stopped if the force on the instructed digit did not exceed 2.5N in the 2s following stimulus onset. Trials were presented in sequential order, starting from the left thumb to the left little finger, and ending with the right thumb to the right little finger. Trials were grouped as blocks, with each block consisting of one measurement each of the four target force levels across the 10 fingers (a total of 4x10=40 trials/block). Each participant performed 4 such blocks during each measurement session.

Quantifying the degree of mirror movements

Participants attempts to produce isometric force with the instructed finger resulted in subtle forces on the fingers of the passive hand (Fig. 1B). These mirrored forces were substantially smaller than the forces produced by the instructed finger. Even at the lowest

target force levels, the trajectory of these averaged mirrored forces correlated strongly with those produced on the instructed finger (Fig. 1C). This was true for both controls (r=0.63, 95% confidence interval, 0.53-0.72), and patients (r=0.61, 0.56-0.65). These correlations increased monotonically as the target force level increased, consistent with previous reports that mirrored forces are a function of the force applied with the active hand (Armatas *et al.*, 1996; Todor and Lazarus, 1986).

To quantify the peak forces produced during mirror movements, first the resting baseline force on each finger prior to movement was subtracted from the subsequent force trace produced during the trial. Then the peak force F_{peak} on the passive hand was calculated as the maximal force on the fingers during the course of the trial:

$$F_{peak} = \max_{t}\left(\frac{\sum_{p=1}^{5}\left|\tilde{F}(t,p)\right|}{5}\right)$$

where t is the duration of the trial in seconds, and $\tilde{F}$ are the baseline corrected forces on finger p of the passive hand. Thus, F_{peak} indicates the total amount of force induced on the passive hand when the active finger produces force.

To derive a singular metric of the degree of mirroring across the different target force levels, we conducted a regression analysis to estimate the ratio of the peak force on the instructed finger (Fig. 1B) and the peak passive force (F_{peak}). First, all trials belonging to movements of the same instructed finger in the same hand were grouped together. We plotted the peak force on the active finger on the x-axis and F_{peak} on the passive hand for corresponding trials on the y-axis. We then estimated the best-fit line that described the data points and at the same time went through the origin (Fig. 1D). Sensitivity to outliers was reduced by using robust regression with a b-squared weighting function. To ensure that we were measuring the linear slope specific to mirroring behaviour and not due to spurious finger presses of the passive hand, we only used trials where the correlation between average force trajectories between active and passive hands was ≥0.2 to estimate the linear slope.

Finally, to allow for the use of parametric statistics, the regression slope (i.e. the estimate of the ratio) was log-transformed to make it conform better to a normal

distribution. The log-slope therefore provides a sensitive measure of the amount of mirroring on the passive hand due to movements of the instructed finger *i*. For each participant, the log-slopes associated with the instructed fingers on each hand were averaged to get a composite metric of the degree of mirroring.

Quantifying finger individuation ability

In addition to the mirrored forces, the production of force with the instructed finger also resulted in overt forces on the passive fingers of the active hand (Fig. 1B). These so-called enslaved forces were generally much larger than the associated mirrored forces - and at high force requirements - degraded the participants ability to produce force with just a single finger (Z. M. Li *et al.*, 1998; Zatsiorsky *et al.*, 2000). We quantified the degree of enslaving in exactly the same way as for mirroring, by estimating the log-slope between the peak forces on the instructed and the passive fingers on the active hand respectively. We have previously used this metric to quantify the loss experienced by patients in their ability to individuate their fingers after a stroke (Xu *et al.*, 2016).

Quantifying mirroring across homologous and heterologous finger pairs

One of the aims of the study was to characterize mirroring effects separately across mirror-symmetric (homologous) and heterologous finger pairs. To do so, we first calculated the degree of mirroring across all possible combinations of instructed/passive finger pairs (25 total finger pairs). Mirroring between each finger pair (i, j) was computed in exactly the same way as in the preceding section, by computing the log-slope between the peak force on the instructed finger *i* on the active hand, and the peak force on finger *j* on the passive hand. This pattern of recruitment of passive fingers during mirroring was quantified separately for each participant/measurement session, and will be referred to as the mirroring pattern.

To determine the degree of homologous mirroring, we averaged the resulting log-slopes for mirror-symmetric finger pairs ($i = j$) for each participant. Mirroring across heterologous mirroring was determined by averaging log-slopes for the non-symmetric finger pairs ($i \neq j$).

Estimating changes in mirroring patterns over time

To estimate similarities between mirroring patterns for patients and controls, we first estimated the average mirroring pattern for all controls. This average mirroring pattern for controls was then correlated with the associated mirroring pattern for each patient, separately for each week. The resulting correlations specified the similarities between the patient and control mirroring patterns throughout recovery. Since the mirroring patterns for controls were themselves estimated in the presence of measurement noise, even a perfect match between patient and control mirroring patterns would not result in a correlation of 1. To estimate a noise ceiling for the correlations, we calculated the average correlation of each controls mirroring pattern with the group mean. As a lower bound, each controls mirroring pattern was also correlated with the group mean in which this participant was removed. These upper and lower bounds therefore specify the range of values the correlations between mirroring patterns for control and patients could maximally take given the measurement noise.

Assessing neural activity associated with individuated finger movements (fMRI)

Cortical activity associated with finger movements was measured in controls and patients at the same time points as for the behavioural measurements; five times over the course of a 1-year period.

Participants were instructed to produce individuated finger movements inside an MRI scanner in a protocol similar to the behavioural task. For the fMRI experiment, only four fingers on either hand were tested (ring finger was excluded). Each trial required the production of 3 short isometric force presses with an instructed finger. To begin, the instructed finger for that trial was highlighted in green for 2s. A green line then appeared in the centre of the screen, which was the cue to produce a short isometric force press with the instructed finger within 1.9s. This cue was repeated 3 times for a total of 3 repetitive presses with the instructed finger for that trial. A successful finger press required the production of either 1.8N or 8% of the MVC for that finger, whichever was lower. The green line turned blue to signal a successful finger press. Trials were grouped as experimental runs, with each run consisting of 3 measurements for the 8 fingers across the

two hands (a total of 3x8=24 trials/run). The trials within each run were presented in pseudo-random order, and participants performed 8 blocks at each measurement session.

Functional scans during task performance were obtained on two different 3T Achieva Philips systems (Johns Hopkins University and University of Zürich). Scans were obtained with a 32-channel head coil, using a two-dimensional echo-planar imaging sequence (TR = 2.72s, 32 slices, 126 volumes per run, slice thickness 2.15 mm, 0.15-mm gap, in-plane resolution 2.3 × 2.3 mm^2). Within each imaging run, five randomly interspersed rest phases lasting 13.6–16.3s were inserted. A T1-weighted anatomical scan (3D MPRAGE sequence, 1-mm isotropic, 240 × 256 × 176 mm FOV) was also acquired. Finally, for each participant, a diffusion tensor-imaging (DTI) image (TR=6.6s, 60 slices, 2.2mm slice thickness, 212 x 212 mm FOV), was acquired to help quantify the size and location of lesions in the grey and white matter regions.

Imaging analysis

All functional data was corrected for motion across runs (Diedrichsen and Shadmehr, 2005), and co-registered to the anatomical-T1 image obtained in the first measurement session for the participant (either week 1 or 4). The raw time-series data was then analyzed using a generalized linear model (GLM), with a separate regressor for each finger/hand/imaging run (4 fingers x 2 hands x 8 runs = 64 regressors). The activation for each trial was modelled using a boxcar function (10.88s) convolved with a standard haemodynamic response function. The resulting parameter estimates were then pre-whitened using the GLM residuals to reduce the effects of estimation noise (Walther *et al.*, 2015).

For each participant, the anatomical-T1 image obtained at the first measurement session was used to reconstruct the pial and white-gray matter surfaces using Freesurfer (Dale *et al.*, 1999). Individual surfaces were aligned across participants and were registered to match a template using the sulcal depth map and local curvature as minimization constraints. This process of alignment results in an excellent fit of the fundus of the central sulcus across participants (Fischl *et al.*, 1999).

The anatomical regions of interest (ROIs) were defined on the group surface using probabilistic cytoarchitectonic maps aligned to the average surface (‘Cortical folding

patterns and predicting cytoarchitecture.', 2008). All surface nodes with the highest probability for Brodmann area (BA 4) 2 cm above and below the hand knob were selected as belong to M1. Similarly, nodes in the hand region in S1 were isolated using BA 3a, 3b, 1 and 2 (combined), again 2 cm above and below the hand knob.

The DTI and anatomical-T1 images obtained at the first measurement time for each participant were used to estimate the size and location of lesions in two ROIs: i) cortical grey matter in the sensorimotor cortices (M1/S1) of either hemisphere, and the ii) length of the corticospinal tract superior to the pyramids. Lesion boundaries were determined independently by two neurologists (authors AVF & MB) that were blind to the patients clinical information and task performance. Detailed information about the distribution of lesions in our cohort of patients can be found in (also see methods, Xu *et al.*, 2016).

Finally, the parameter estimates from the M1 and S1 ROIs - that were not identified as part of that patients patients lesion site - were identified and pre-whitened using the GLM residuals to reduce the effects of estimation noise (Walther *et al.*, 2015). These pre-whitened parameter estimates were used as measures of task-specific cortical activation. Since measuring participant data at each of the 5 sessions following stroke was ambitious, we ended up with an unbalanced experimental design due to missing data across the fMRI experiment. We therefore used linear mixed-effects models for the summary plots of the fMRI experiment (Fig 6D; *lme4* package in R; (Bates *et al.*, 2014)) to account for the problem of missing values.

Statistical analysis

Wherever appropriate, we used 2-sided t-tests to test for differences in means either across groups, or across different time-points of recovery. To test for differences between summary statistics across groups or over time, we used linear mixed-effects models in the lme4 package in R (Bates *et al.*, 2014). In all statistical models, an intercept was included as a fixed effect, and each participant was considered a random-effect. All data presented in the text and figures are represented as mean ± standard error of the mean (SEM). All statistical tests involving correlations were performed on Fisher Z-transformed values.

Results

Mirror movements appeared early after stroke and normalized over the year

Using a sensitive behavioural assay, we quantified mirror movements in 53 patients with stroke and 14 age-matched controls. The first measurement was within the first 2-weeks of the insult, and at four subsequent sessions distributed over the course of a year (for schedule see Table 1). During each measurement session, patients and controls produced individuated finger presses at different target force levels while forces on the passive hand were measured (Fig 2B). To quantify the degree of mirroring, we calculated the linear slope between the peak forces produced by the instructed finger and the peak averaged forces on the passive hand (Fig 1D; see methods).

Patients showed large time-course changes in mirroring in the year following a stroke (Fig. 2A). In the first two weeks after damage (week 2), individuated finger presses with the paretic hand resulted in large forces in the non-paretic hand with 1N of applied force resulting in approximately 0.051N of averaged mirrored force. In comparison, mirroring in controls was very low (1N resulted in 0.004N mirroring) with the difference to patients being highly significant at this time point (t_{51}=3.67, p=0.001). Mirroring in patients subsequently reduced over time (χ^2=82.99, p<<0.0001). However - even 6 months after the original injury - mirroring was still marginally larger in comparison to controls (t_{51}=1.75, p=0.087). There was a strong association between mirroring during the early and late stages following stroke r=0.73 (p<0.001), demonstrating that patients who exhibited large mirroring early after stroke continued to do so throughout recovery.

The longitudinal changes in mirror movements were remarkably similar to those for the deficits in fine-finger function in the paretic hand (Fig. 2B). After a stroke, patients efforts to produce isometric forces with a single finger resulted in abnormally large forces on the passive fingers of the paretic hand. These enslaved forces are a measure of the loss in fine-finger control in patients (S. Li *et al.*, 2003; Xu *et al.*, 2016). Early after damage (week 2), enslaving in patients was significantly larger than for controls demonstrating a substantial loss of individuated finger control (controls 0.042N/1N; patients 0.170N/1N; t_{51}=4.02, p<0.001). Enslaving progressively reduced over the course of the year (χ^2=28.38, p<<0.0001), but never fully normalized even by 6 months post stroke (t_{51}=3.09, p=0.003).

Patients who had large enslaving early after stroke also demonstrated large mirroring at the same time-period (enslaving and mirroring at week 2, $r=0.78$, $p<<0.0001$), and continued to do so even by the chronic stage of recovery (enslaving week 2 and mirroring week$\geq$24, $r=0.66$, $p=0.0001$).

Overall, although the longitudinal changes for both mirroring and enslaving were very similar, the appearance of mirror movements early after stroke (week 2) demonstrates that the phenomenon is not the by-product of a compensatory response by the brain in order to recover paretic hand function.

Characterizing the homologous and heterologous components of mirroring

Next, we were interested in quantifying the nature of mirroring movements on the non-paretic hand. Specifically, we wanted to determine whether individuated finger presses with the paretic hand resulted in the mirroring primarily on the mirror-symmetric (homologous) finger, or rather a broad recruitment of fingers in the non-paretic hand. Such focal or broad patterns of mirror movements would indicate the involvement of cortical and subcortical pathways respectively (see introduction). We therefore characterized patterns of mirroring (see methods) in both controls and patients

The degree of mirroring for each passive finger as a function of the finger pressed on the active hand can be seen in Figure 3A. The overall patterns of mirroring across all active/passive finger pairs themselves were highly reliable, with split-half correlations being $r>0.85$ for both controls and patients (Supplementary Table 1). The first immediate observation is that mirroring was not restricted to the homologous fingers (diagonal), but that substantial effects could be observed on heterologous fingers (off-diagonal) as well. To quantify this observation, we partitioned mirroring across the different active/passive finger pairs into their respective homologous and heterologous components (see methods).

In controls, finger presses resulted in a broad recruitment of fingers in the passive hand. Finger presses with the active hand were highly individuated in nature, with 1N of force on the instructed finger resulting in 0.042N of enslaved forces on the same hand (ratio of 24.77±2.18 Fig. 2B). In turn, these finger presses resulted in mirroring across both homologous and heterologous fingers pairs. While homologous mirroring was, on average, larger than the heterologous component ($t_{13}=5.421$, $p=0.0001$), some finger presses resulted

in near equivalent effects on both (index finger presses; t_{13}=1.23, p=0.240, ring; t_{13}=0.88, p=0.398). Overall, forces on the passive hand were much less fractionated in nature than the forces on the active hand (Fig. 3B), with the corresponding ratio between homologous and heterologous mirroring components (1.61±0.16) being nearly 5 times smaller than the instructed/enslaving ratio on the active hand (t_{13}=28.26, p<<0.0001).

Similarly, in patients, finger presses with the paretic hand resulted in a broad recruitment of fingers in the non-paretic hand. The year-long changes in mirroring characterized earlier (Fig. 2A) were observed for both the homologous and heterologous components (Fig. 3C; change over weeks: homologous, χ^2=71.35, p<<0.0001, heterologous, χ^2=78.15, p<<0.0001), with the homologous component being the stronger of the two (χ^2=24.53, p<<0.0001). Critically, despite these longitudinal changes, the ratio between the homologous and heterologous components (1.76±0.12) remained stable across weeks (χ^2=1.16, p=0.885) and at the same level as for healthy controls (χ^2=0.10, p=0.754). Through recovery, mirrored forces on the non-paretic hand were less fractionated in comparison to the finger presses on the paretic hand that caused them (Fig. 3D; χ^2=271.2, p<<0.0001). To summarize, during finger presses in patients – like controls – resulted in a broad recruitment of fingers on the passive hand, yet mirroring effects were slightly larger on the homologous as compared to the heterologous component.

Altogether, our results raise an interesting paradox. On the one hand, performing an individuated finger press requires input from cortical motor areas (Diedrichsen *et al.*, 2013). If activities in these cortical areas spill over onto motoneurons/spinal interneurons controlling the passive hand, it would predict mirroring primarily on the mirror-symmetric homologous finger, which is not the case. On the other hand, homologous mirroring is consistently larger than the associated heterologous component. Such a pattern of mirroring is difficult to attribute solely to the action of subcortical pathways given their limited ability to control distal hand muscles in a fractionated fashion (Lawrence and Kuypers, 1968b; Soteropoulos *et al.*, 2012). The most parsimonious explanation of these mirroring patterns is that they represented summed contributions from both cortical and subcortical motor circuits involved in hand function.

A closer examination of the nature of mirror movements in the paretic hand provided further evidence for this view (Supplementary Figure 2). If the homologous

component of mirroring is primarily contributed by cortical motor areas, stroke-related damage in the lesioned hemisphere might result in a less fractionated pattern of mirroring on the paretic hand in comparison to that seen on the non-paretic hand. As predicted, the degree of mirroring across homologous and heterologous finger pairs in the paretic hand was approximately equal in the period early after stroke (Supplementary Figure 2B; week 2; ratio=1.11±0.11). The pattern of mirroring across fingers became progressively more fractionated in nature as the paretic hand regained fine-finger function, with the ratio between homologous and heterologous mirroring increasing during recovery (χ^2=21.47, p=0.0003), and eventually normalizing to the level of controls (week≥24; t_{36}=0.48, p=0.632).

No modulation of evoked-BOLD activities in the bilateral sensorimotor cortices after stroke

Finally, we conclude with a consideration of the neurophysiological mechanisms that could cause an exaggeration of mirror movements after stroke. One clue came from a closer inspection of mirroring across all active/passive fingers, irrespective of whether the fingers pairs belonged to the homologous or heterologous components (Fig. 3A, 4A). A remarkable similarity between patients and controls was observed. On average, the patterns for patients looked like a scaled version of the corresponding pattern in controls, resulting in a constant offset in the y-axis in our log-scaled plot. Similarity between the patterns for patients and controls was high, even in the early period after stroke (r=0.88, p<<0.0001), with this similarity between patterns remaining unchanged throughout recovery (Fig. 4B; χ^2=1.87, p=0.760). This suggests that the patterns of mirroring for controls and patients were - up to a scaling factor - identical.

This similarity between mirroring patterns across groups suggests that whatever motor system(s) is responsible for generating mirror movements in health, it is largely (un)up-regulated after a stroke. One candidate mechanism could be the large activations previously reported in the primary somatosensory (S1) and motor (M1) cortices of the non-lesioned hemisphere after a stroke (Cincotta and Ziemann, 2008) (Cramer *et al.*, 1997; Y.-H. Kim *et al.*, 2003; Ward *et al.*, 2003; Wittenberg *et al.*, 2000). These activations could cause exaggerated mirror movements either directly or indirectly. In the first case,

activations could be directly transmitted to the motoneurons/spinal interneurons that control the passive hand, via the crossed corticospinal pathway. Alternatively, the activations could indirectly exaggerate mirroring by up-regulating the activity of subcortical motor circuits through cortico-brainstem connections (Fisher *et al.*, 2012).

If mirror movements after stroke were caused by over-activation of the non-lesioned sensorimotor cortex, then the time-course of these cortical activations should resemble those for the changes in mirroring quantified earlier (Fig. 2A). To test for evidence of this, we used functional magnetic resonance imaging to measure the evoked activities in the hand areas of S1 and M1 in the same cohort of patients. For this experiment, only 35 patients and 12 controls could be measured (fMRI; Table 1). Both patients and controls were instructed to perform individuated finger presses with their paretic hand inside an MRI scanner (Fig. 5A), with an experimental design that was very similar to that used to quantify mirror movements in the behavioural experiment (see methods). We confirmed that patients continued to demonstrate the same mirroring and enslaving behaviour both inside and outside the scanner environments (Fig. 5B-C; inside versus outside: mirroring, $r=0.89$, $p<<0.001$; enslaving, $r=0.75$, $p<<0.001$).

The resulting evoked BOLD responses in the sensorimotor cortices for patients were remarkably stable throughout recovery (Fig. 6D; statistics in Table 2). For paretic hand presses, we did not find any time-course related changes in the evoked-activities in either the contra- or the ipsilateral sensorimotor cortices, with the activations in either hemisphere indistinguishable from counterpart activations in controls. Patients continued to demonstrate the stereotypical pattern of evoked cortical responses seen for unimanual finger presses in health; an increase and reduction of BOLD responses in the contra- and ipsilateral sensorimotor cortices respectively.

To summarize, here we report that the clear occurrence of the longitudinal changes in mirror movements after stroke were not accompanied by dysfunctional activations in the sensorimotor cortices of either the non-lesioned or the lesioned hemispheres. The sensorimotor areas measured here (M1 and S1) provide the bulk of the input to the corticomotor pathways that facilitate fine-motor function of the hand (Lemon, 2008; Porter and Lemon, 1993). The lack of activity modulation in these areas suggests that a simple

up/down regulation of overall cortical sensorimotor activations is not the mechanism by which mirror movements are exaggerated after stroke.

Discussion

In this study, our first aim was to provide a detailed characterization of the longitudinal changes in mirror movements following stroke. Consistent with earlier findings, mirror movements only exaggerated on the non-paretic hand (Y.-H. Kim *et al.*, 2003; Nelles *et al.*, 1998; Sehm *et al.*, 2009; Wittenberg *et al.*, 2000). We expand upon these previous studies and demonstrate that mirror movements appear early after stroke. This early appearance largely rules out mirroring as a by-product of the brain attempting to reorganize and restore function to the paretic hand. The most likely possibility is that damage in a single hemisphere results in abnormal input to the motoneurons and spinal interneurons that control the non-paretic hand. Since we found no evidence of over-activations in the sensorimotor cortices that provide the bulk of input to the corticospinal pathways, its unlikely that direct excitatory corticospinal input to the non-paretic hand, from either hemisphere, is the sole cause for the exaggeration of mirror movements early after stroke.

Our second study aim was to better understand the nature of mirroring across the passive hand, both in health and after stroke. Specifically we were interested in characterizing the degree to which individuated finger presses result in forces on mirror-symmetric homologous and/or heterologous finger pairs. Although recent reports on mirror movements have mostly focused on the homologous muscles/fingers (Armatas *et al.*, 1994; Y. Kim *et al.*, 2015; Koerte *et al.*, 2010; Mayston *et al.*, 1999), the earliest reports have reported heterologous effects as well, especially on the antagonist muscles (E. Fog and M. Fog, 1963; Hellebrandt and Waterland, 1962; Missiuro, 1963; Todor and Lazarus, 1986). Our results demonstrate that homologous mirroring, at least in the context of finger movements, is a small but important component of the overall mirroring on the passive hand. That the ratio between the homologous and heterologous components is not a fixed value (see mirroring in paretic hand; Supplementary Figure 2), makes it unlikely that the heterologous mirroring component represents small extension forces that are required to recruit muscles in such a way as to produce mirroring purely on the homologous finger.

The most parsimonious explanation of the pattern of recruitment of fingers during mirroring is that motor circuits in both cortical and subcortical combine to produce the phenomenon.

An interesting side-observation obtained from studying mirroring movements is that subcortical pathways involved in hand function appear to be under direct cortical control. None of the patients in our cohort had lesions in the brainstem areas, yet significant corticospinal damage completely abolished any mirror movements in the paretic hand. This would not be the case if subcortical pathways were capable of being activated independently from cortical areas in order to move the hand. Our findings are consistent with reports in primates that have demonstrated direct cortical influence on subcortical pathways involved in finger movements (Fisher *et al.*, 2012).

Although lesion studies in primates have dissected the role of subcortical pathways in hand function in great detail (Baker, 2011b; Lawrence and Kuypers, 1968b; Riddle *et al.*, 2009; Soteropoulos *et al.*, 2012; Zaaimi *et al.*, 2012), the extent to which these subcortical pathways are also involved in humans remains to be determined. One clue comes from comparing the patterns of upper-limb muscle recruitment during mirroring movements in humans with the muscle responses observed during the activation of different subcortical motor pathways in primates. Previously, Missouri (1963) demonstrated in 3-6 year old children, that flexion of the elbow joint resulted in mirroring mostly on the antagonist extensor muscles of the elbow of the opposing limb. This pattern of facilitation of ipsilateral flexors and contralateral extensor shoulder muscles is a prominent pattern of evoked-muscle activity observed during stimulation of neurons in the ponto-medullary reticular formation (Herbert *et al.*, 2010; Hirschauer and Buford, 2015). Neurons in this area provide input to the reticulospinal tract, which along with the rubrospinal tract makes up the two major descending subcortical motor pathways originating in the lateral and medial aspects of the brainstem respectively (Lawrence and Kuypers, 1968a; 1968b). Of these two, while the lateral (rubrospinal) tract is largely absent in man (Nathan and Smith, 1955), the medial (reticulospinal) tract has been strongly implicated as a parallel pathway involved in the facilitation of hand function (Baker, 2011a; Riddle *et al.*, 2009; Soteropoulos *et al.*, 2012) and can therefore serve as a subcortical motor pathway capable of contributing towards the generation of mirror movements.

If recovery of paretic hand function relies increasingly on the capacity of subcortical circuits to compensate for cortical damage (Xu *et al.*, 2016), and if these subcortical circuits are responsible for contributing towards mirror movements, then how do mirror movements reduce over the same time while paretic hand function recovers. Although subcortical pathways generally project bilaterally to either half of the spinal cord (Sakai *et al.*, 2009) and produce simultaneous activity across both upper-limbs (Hirschauer and Buford, 2015), we suggest that an increased reliance on these subcortical pathways for recovery need not have a detrimental impact on mirror movements. In primates, neurons in the ipsi- and contralateral sections of the ponto-medullary reticular formation (PMRF) have been shown to alter the strength of their output onto motoneurons/spinal interneurons in either half of the spinal cord independently (Herbert *et al.*, 2015). Thus cells in the PMRF ipsilateral to the paretic hand could strengthen connections to the paretic hand in order to provide compensatory control, while cells in contra-PMRF independently alter their connections to the spinal cord to reduce mirror movements in the non-paretic hand.

Funding

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Tables and Figures

week	2	4	12	24	52
days (mean±SD)	10 ± 4	37 ± 8	95 ± 10	187 ± 12	370 ± 9
Behavioural experiment	**53 patients, 14 controls**				
measured at week (%)					
controls	14 (100%)	10 (71%)	12 (86%)	12 (86%)	12 (86%)
patients	39 (74%)	39 (74%)	40 (75%)	39 (74%)	31 (58%)
Fugl-Meyer (0.25-0.75 percentile)	(16-59)	(34-64)	(52-66)	(57-66)	(59-66)
fMRI experiment	**35 patients, 12 controls**				
measured at week (%)					
controls	11 (92%)	10 (83)	11 (92%)	11 (92%)	11 (92%)
patients	24 (69%)	31 (89%)	27 (77%)	28 (80%)	19 (54%)
Fugl-Meyer (0.25-0.75 percentile)	(16-60)	(45-65)	(59-65)	(60-66)	(64-66)

Table 1. Patient information and measurement schedules for the behavioural and fMRI experiments. A total of 53 patients and 14 age-matched controls were recruited for the study and measured at five different time points over the course of a year. For the behavioural experiment, each participant in the study was on average measured over at least 3 sessions (patients, 3.5±1.5 sessions; controls, 4.3±1.4), with the overall experimental data being 70.1% complete for patients and 85.7% complete for controls. For the fMRI experiment, a subset of participants from the cohort were measured (N=12 controls and N=35 patients), with the experimental data being 73.7% complete for patients and 90% for controls.

	change over weeks		patients versus controls	
	$\chi 2$	p	$\chi 2$	p
activity for paretic presses				
contra (S1)	1.410	0.842	1.160	0.282
contra (M1)	2.070	0.723	1.150	0.285
ipsi (S1)	1.860	0.761	0.813	0.367
ipsi (M1)	1.250	0.870	0.010	0.915

Table 2. Statistics for the fMRI experiment. Statistics are shown for differences in contralateral and ipsilateral M1/S1 activations, across weeks (first two columns) and between patients and controls (last two columns).

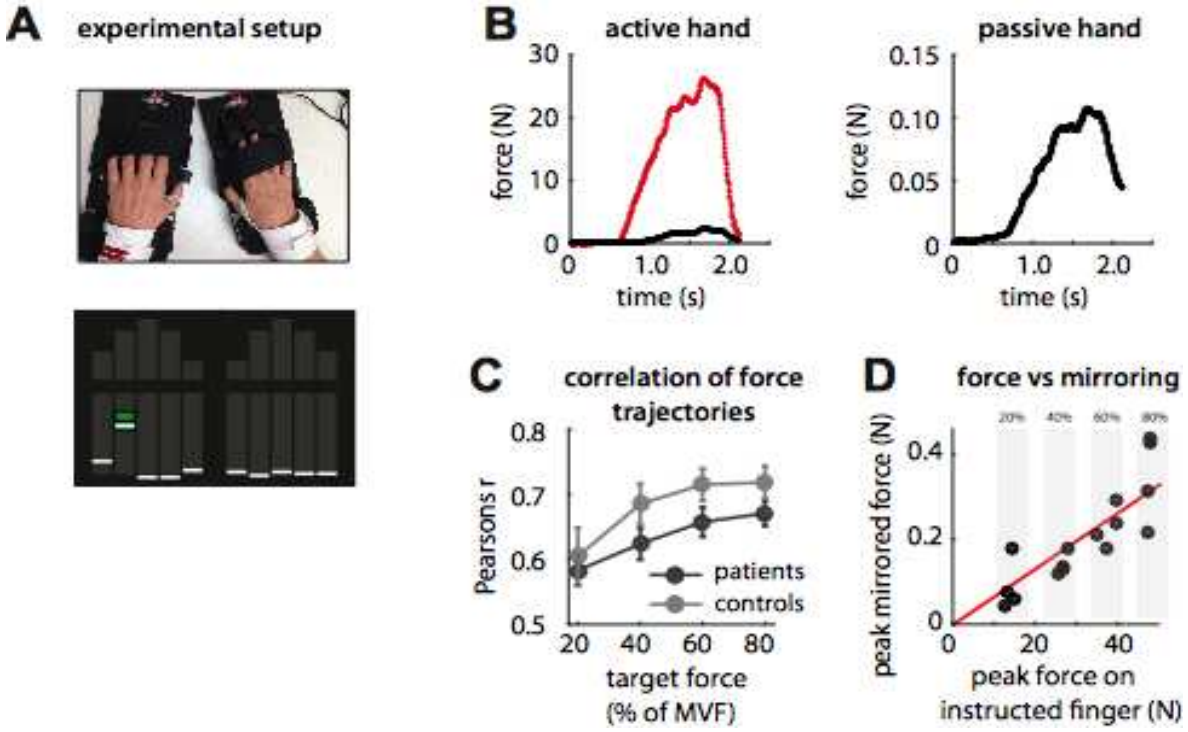


Figure 1. Assessment of mirror movements. (A) Both hands were strapped onto an ergonomic hand device capable of measuring isometric forces generated at the fingertips, and controls and patients were instructed to generate isometric forces by making individuated presses to bring the cursor into the target zone shown in green. During each measurement session, individuated forces presses were made at 20%, 40%, 60% and 80% of the maximum voluntary force on that finger. (B) Force presses with the instructed finger (thumb finger of right hand shown in red) resulted in involuntary forces on the passive fingers of the same hand (black), and subtle mirrored forces on the fingers of the passive hand (right panel). (C) Mirrored force trajectories were similar to that for the instructed finger, especially at higher target force levels. (D) Mirroring was quantified as the linear slope between the peak forces produced by the instructed finger and the peak averaged forces on the passive hand. The linear slope was log-transformed to allow the use of parametric statistical test, but for the purpose of clarity the raw values of the linear slope are reported in all subsequent figures.

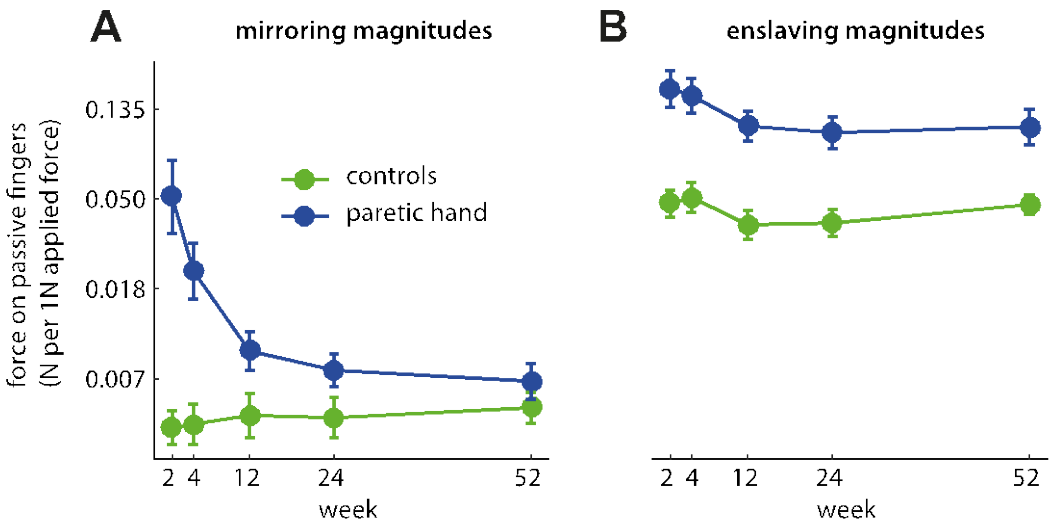


Figure 2. Longitudinal changes in mirror movements and fine-finger control after stroke. (A) Changes in mirroring for controls and patients measured over the course of a year. For patients, mirroring was measured in the fingers of the non-paretic hand, during active finger presses with the paretic hand. (B) Associated changes in fine-finger control on the active hand across groups. Individuated finger presses in patients and controls resulted in undesired force contractions on the uninstructed fingers of the active hand. The larger these so-called enslaved movements, the worst the degree of fine-fine control. For clarity, the raw values of the linear-slope estimates for mirroring and enslaving are plotted in (A) and (B).

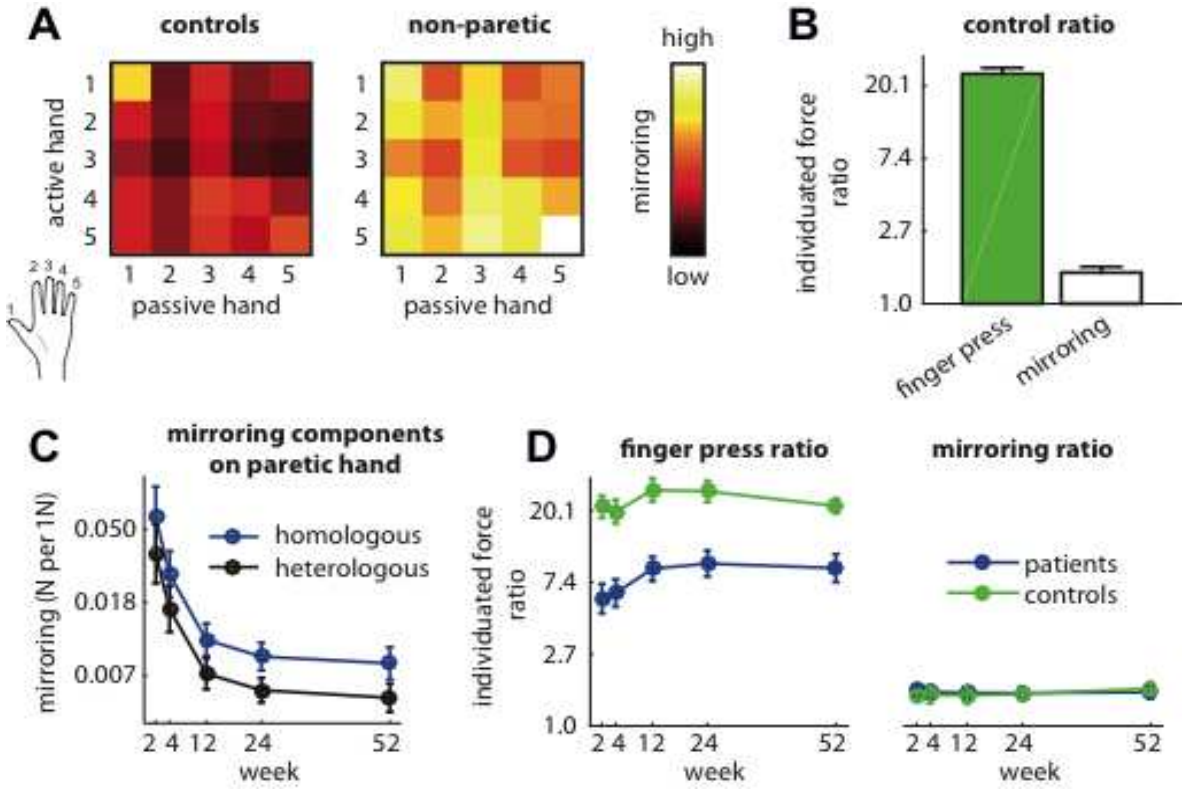


Figure 3. Relative contributions of homologous and heterologous components to mirror movements on the non-paretic hand. (A) Mirroring across all possible active/passive finger pairs for controls and patients (on non-paretic hand only). Rows and columns denote which finger was pressed on the active hand, and the finger on the passive hand that mirroring was estimated on, respectively. Diagonal and off-diagonal matrix entries represent mirroring across homologous and heterologous finger pairs. (B) Individuated finger presses by controls resulted in enslaved forces on the passive fingers of the same hand and mirrored forces across homologous and heterologous finger pairs. The ratio between instructed/enslaved forces is shown in green, while ratio between homologous and heterologous mirroring components is shown in white. (C) Changes in homologous and heterologous mirroring components on the non-paretic hand in the year following stroke. For clarity, the raw values of the linear-slope estimates for mirroring are plotted. (D) For patients, the ratios between instructed/enslaved forces on the paretic hand, and the ratio between homologous/heterologous mirroring patterns are shown in the left and right panels respectively.

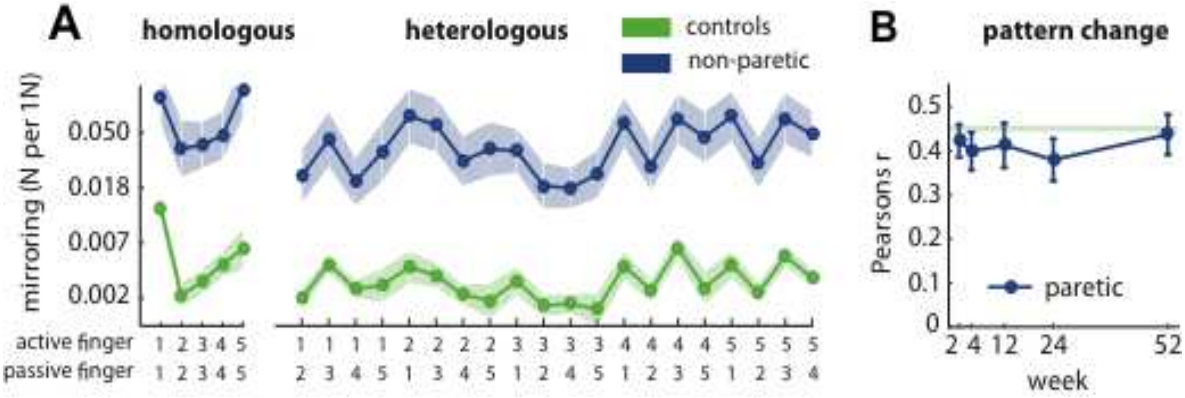


Figure 4. Stability of mirroring pattern during stroke recovery. (A) The average mirroring patterns across all active/passive finger pairs are shown for patients and controls. For clarity, the raw values of the linear-slope estimates for mirroring are plotted in A. (B) Correlation between mirroring patterns for patients and controls over the course of the year. The pattern correlations for patients and controls were close to noise ceilings; i.e. the maximum possible pattern correlations possible given the measurement noise on mirroring patterns for each control (see methods).

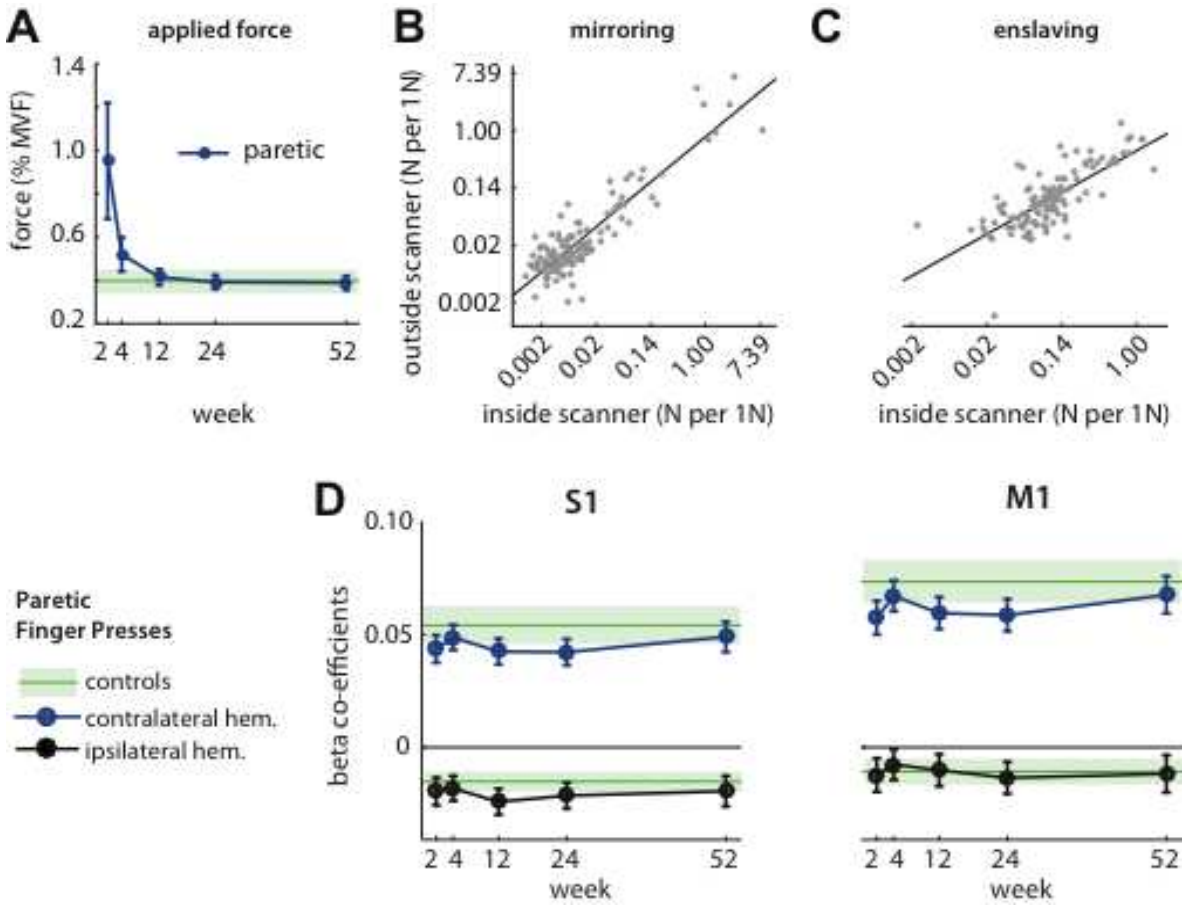
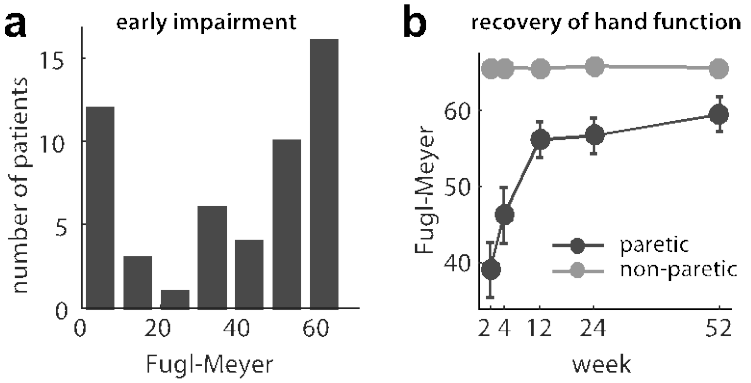


Figure 5. Evoked-BOLD activities for finger presses in the primary somatosensory (S1) and motor (M1) cortices. (A) During the fMRI task, patients and controls were required to produce either 1.8N or 8% of the maximum voluntary force (MVF) on the finger. Forces are expressed as a percentage of MVF. Controls produced forces at approximately 40% of MVF. From week 2 onwards, forces produced by patients and controls were matched (week≥4; χ^2=0.02, p=0.887). (B) Measurements of mirroring on the non-paretic hand were highly correlated inside and outside the scanner environments. (C) Similarly, enslaving in the paretic hand was highly correlated for measurements inside and outside the scanner environments. Each dot in B-C represents the session measurement of a single patient. For clarity, the raw values of the linear-slope estimates for mirroring are plotted in (B-C). (D) Evoked-BOLD activities in contra- and ipsilateral S1 and M1 cortices due to paretic finger presses. Corresponding contra and ipsi activities in controls are depicted by the shaded green regions (Mean±SE).

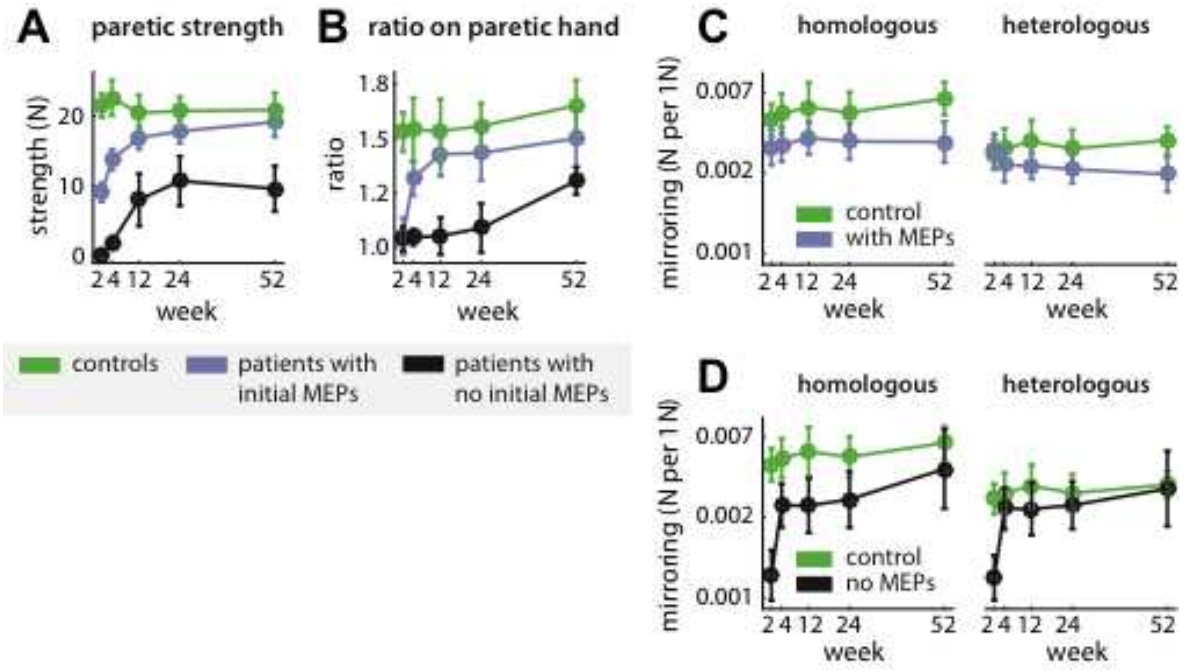
Supplementary Material

week	2	4	12	24	52
controls					
mean	0.88	0.89	0.90	0.89	0.92
range	(0.82-0.92)	(0.85-0.92)	(0.85-0.94)	(0.84-0.93)	(0.88-0.94)
non-paretic hand					
non-paretic hand	0.86	0.89	0.89	0.90	0.89
range	(0.82-0.89)	(0.86-0.92)	(0.86-0.91)	(0.86-0.92)	(0.85-0.92)
paretic hand					
paretic hand	0.88	0.87	0.87	0.90	0.87
range	(0.83-0.90)	(0.84-0.90)	(0.84-0.90)	(0.88-0.92)	(0.82-0.91)

Supplementary Table 1. Split-half reliabilities for mirroring patterns estimated across weeks. To estimate the reliability, data from each measurement session was dividing into odd and even runs, and the corresponding mirroring patterns for each half were estimated independently. Pearson's correlation between the patterns from the two halves was then calculated to obtain the within-session or split-half reliability.



Supplementary Figure 1. Patient information. (a) Distribution of Fugl-Meyer measurements on paretic hand at the point of first measurement (either week 2 or 4). (b) Fugl-Meyer measurements for patients over the course of 1 year following stroke.



Supplementary Figure 2. The homologous and heterologous components of mirror movements in the paretic hand. (A) Time course of strength recovery in patients who demonstrated reliable MEPs (mild group) in the first few weeks after stroke, and those who did not (severe group). (B) Ratios between the homologous and heterologous mirroring components across the mild and severe groups. (C) The homologous and heterologous mirroring components for controls and the mild group. (D) The homologous and heterologous mirroring components for controls and the severe group. For clarity, the raw values of the linear-slope estimates for mirroring are plotted in (C-D).

In the main text, we primarily focus our analysis on mirror movements in the non-paretic hand. In addition, after stroke a mild reduction in mirror movements in the paretic hand has previous been reported (Nelles *et al.*, 1998). Here, we characterize mirroring effects on the homologous and heterologous finger pairs in the paretic hand. Since the degree of mirroring in the paretic hand might be influenced by the loss of strength on the hand, we restricted our analysis to a subset of relatively mildly impaired patients (N=29). Patients into a mild and severe group based on whether or not reliable muscle potentials could be evoked on the paretic hand during transcranial magnetic stimulation of the lesioned hemisphere. Only TMS measurements obtained within the first 2 weeks after

stroke were used to categorize patients. During each measurement session, 10 single TMS pulses were applied to the hand area of the motor cortex in the lesioned hemisphere while muscle activity from the contralateral FDI muscle was recorded. Patients that were able to demonstrate reliable muscle evoked-potentials (MEP≥50μV) for at least 5 out of the 10 TMS pulses were placed into the mild group, while those that did not show reliable muscle potentials even at 100% stimulation intensity were categorized into the severe group. For this experiment, only a subset of 40 patients (Fugl-Meyer, 16-59, 25%-75% percentile) were measured. 11 patients did not demonstrate reliable MEPs at week 2 and were thus categorized as severe.

29 patients categorized as mild and we focused our mirroring pattern analysis on this subgroup. Even in the early period after stroke, patients in this subgroup had sufficient residual strength to be able to express mirroring at the level of controls (0.004N mirrored force for 1N applied). At maximal force contractions with the non-paretic hand (15.7N), the predicted mirrored forces on the paretic hand were small (0.07N) in comparison to the residual strength on the hand (9.0N; residual strength versus predicted mirroring at control level, t_{21}=6.77, p<<0.0001).

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